The Report Committee for Li Wang
certifies that this is the approved version of the following report:

Identification of Optimal Moderators in Clinical Trials

APPROVED BY

SUPERVISING COMMITTEE:

Michael Daniels, Supervisor

Peter M*ü*ller

Identification of Optimal Moderators in Clinical Trials

by

Li Wang, B.S.

REPORT

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE IN STATISTICS

THE UNIVERSITY OF TEXAS AT AUSTIN

May 2015

Identification of Optimal Moderators in Clinical Trials

Li Wang, M.S.STAT.
The University of Texas at Austin, 2015

Supervisor: Michael Daniels

Moderators and mediators can be very informative in the analysis of clinical trials to help determine what treatment should be assigned to individuals (moderators) and to determine how to improve treatments (mediators). It is well known that a treatment might not be equally beneficial to everyone and an overall effective treatment may be less effective (or even harmful) in certain groups; this highlights the importance of moderators in making treatment assignment decisions. A combined moderator, or optimal moderator, can be useful when multiple potential moderators exist, but no individual one is particularly strong. This report reviews how to assess a single moderator as well as approaches to derive an optimal moderator. An example from randomized clinical trial is presented, including the identification of an optimal moderator.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction: A Brief Review of Moderators and Mediators

Consider a single-blind, multi-site, randomized controlled trial (RCT) with outcome O and two treatments $T(T1$ and $T2)$, and the baseline variable M. M is a moderator if it helps explain under which circumstances that T is related to O while M is a mediator if it helps explain how or why T is related to O (Baron and Kenny, 1986).

Differences and similarities between moderators and mediators were further discussed in Kraemer et al. (2013). More specifically, M is a moderator if it is uncorrelated with T and the correlation between T and O differs by M. On the other hand, M is a mediator if it is correlated with T and the correlation between T and O can be partly explained by the effect of T on M. The relationship among T, M, and O in these two cases are shown in Fig 1.1.

From the definition above, a variable cannot be both a moderator and mediator. Moderators help determine which group of patients should receive which treatment to optimize the outcome, and mediators explores how a treatment works on the outcome so that it is feasible to improve or remove some treatment to make it more effective or cost less. Baseline covariates are poten-

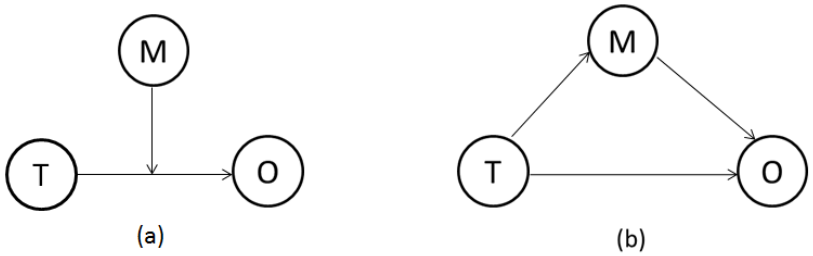

Figure 1.1: (a)Moderation of M on T and O ; b)Mediation of M on T and O

tial moderators, since by randomization, they are uncorrelated with treatment.

In this report, we focus on the moderators to choose a suitable treatment for different groups of patients in order to benefit them. Chapter 2 introduces the effect size calculation and measurement for a single moderator, based on a linear regression approach with interaction term included. Chapter 3 discusses methods to obtain an optimal moderator when multiple potential moderators exist, to strengthen the moderation as well as make it more convenient for treatment assignment decisions. Moderators and optimal moderators are implemented by an example in Chapter 4, where the data from an RCT is used and several baseline covariates are primarily selected and discussed.

Chapter 2

Parametric approach for accessing moderators

2.1 Introduction to effect size and Cohen′s d

2.1.1 Basic Definitions

The term effect size generally refers to a statistic which measures the strength of a treatment effect. One of the advantages of effect size measurement is that it does not depend on the sample size of the data, which is quite different than that of the traditional significance testing. Note that effect size is typically standardized if outcomes and independent variables are measured on different scales, or the results come from different experiments.

According to the website of Becker, these methodologies can be summarized into two ways to measure effect size:

1. **Using standardized difference between two means**

2. **Using effect size correlation**

   The effect size correlation is the correlation between the independent variable and the dependent variable, such as outcome (Rosnow & Rosenthal, 1996).

In terms of using standardized difference between two group of means, Cohen′s d (Cohen, 1988) is a typical method. Define d as the standardized difference of two means, during the process of which either standard deviation of the two groups can be used if the variation from the two groups is homogeneous. It is defined as

$$d = \frac{M_1 - M_2}{\sigma}$$
$$\sigma = \sqrt{\frac{\sum_i^n (X_i - M)^2}{n}},$$

where M_1, M_2, M are two group means and overall mean respectively, X is group, and n observations; d denotes Cohen′s d.

In practice, it is common to apply σ_{pooled} as the pooled standard deviation calculated from two independent groups. Cohen′s d is then defined as

$$d = \frac{M_1 - M_2}{\sigma_{pooled}}$$
$$\sigma_{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$
$$s_i^2 = \frac{1}{n_i - 1} \sum_{j=1}^{n_i} (m_{i,j} - M_i)^2, \quad i = 1,\ 2,$$

where n_1 and n_2 are the number of data for each group, and $m_{i,j}$ are the observed data from each group i, i=1,2.

On the other hand, considering using effect size correlation, it is quite common to use Pearson product-moment correlation as the value of effect size correlation. Suppose X denotes the independent variable and Y denotes the dependent variable, the Pearson product-moment correlation r_{XY} is defined as

$$r_{XY} = \frac{Cov(X, Y)}{\sigma_X \sigma_Y}$$

Note that the effect size correlation can also be calculated from Cohen′s d as follows:

$$r_{XY} = \frac{d}{\sqrt{d^2 + 4}}$$

2.1.2 Interpretation of Effect Size and Cohen′s d

Based on the definition from Cohen (1988), there are three levels of the strength for effect size:

1. **d = 0.2, small**
2. **d = 0.5, medium**
3. **d = 0.8, large**

Effect size can be viewed as the percent of nonoverlap of the one treatment group's scores with those of another treatment group. For example, d =

0.0 shows that there is 0 percent of nonoverlap between the two treatments, or we could say the two groups overlap completely. d = 0.5 indicates that there is 33.0 percent of nonoverlap between two treatment groups. d = 0.8 states that there is 47.4 percent of nonoverlap between two treatment groups. Note that d can be greater than 1 but the percent of nonoverlap should stay betwen 0 and 1.

2.2 Moderator effect size

Linear regression models are an effective and popular approach to determine whether a variable is a moderator or not. Let O denote the outcome variable, and T represent treatment. The linear regression model is

$$O = b_0 + b_1 T + b_2 M + b_3 T * M + \epsilon. \tag{2.1}$$

Note that interaction term allows the treatment to have a different effect on the outcome depending on M. M can be either continuous or categorical, and the interaction term $T * M$ is of primary interest. The error term ϵ, which is independent of treatment and M, follows a normal distribution, $N(0, \sigma^2)$.

To interpret the coefficients of linear model above, b_0 is the intercept; b_1, the main effect; b_2, the effect of M; and b_3, the interaction effect of T under M.

To be specific, there are three possible cases for M: non-predictor, predictor but non-moderator, and moderator. These are detailed in the explanation and figures below. In the figure, the x-axis denotes M and the y-axis,

the outcome. The vertical distance between two lines indicates the effect size difference between the two treatments at a certain value of M.

1. **M: Non-predictor in both treatment groups** (T1 and T2)

   The linear regression model is

   $$\begin{aligned} O &= b_0 + b_1 T + (0 \times M + 0 \times T * M) + \epsilon \\ &= b_0 + b_1 T + \epsilon. \end{aligned}$$

   It is the simplest model where the interpretation of coefficients is straightforward. Since there is no effect of M, b_1 shows the amount change of outcome on average for the change in treatments. Also, see Figure 2.1.

2. **M: Predictor but non-moderator in both treatment groups** (T1 and T2)

   Now suppose that $T1$ responds to a higher level of the outcome then $T2$ by M. In this case, it is shown in Fig 2 that the difference in the outcome between $T1$ and $T2$ is constant under M. That means, M is a predictor of the outcome under both treatments, but the effect size is the same for all values of M. Then the linear regression model is:

   $$\begin{aligned} O &= b_0 + b_1 T + b_2 M + (0 \times T * M) + \epsilon \\ &= b_0 + b_1 T + b_2 M + \epsilon. \end{aligned}$$

   Here b_2 represents the main effect of M, which is additive to the effect of treatment, b_1.

3. **M: Moderator in both treatment groups** (T1 and T2)

   Another scenario occurs when $T1$ has a steeper M-outcome curve than $T2$, or vice versa (Fig 2.3 and Fig 2.4). In both cases, the effect size of treatment changes; thus M is a Moderator.The true linear regression model is:

$$O = b_0 + b_1 T + b_2 M + b_3 T * M + \epsilon.$$

   This is a more complex model since there are interaction effects between treatment and moderator on the outcome. b_3 represents the slope differences of the two line, $T1$ and $T2$. The effect of treatment on O is $b_1 + b_3 M$.

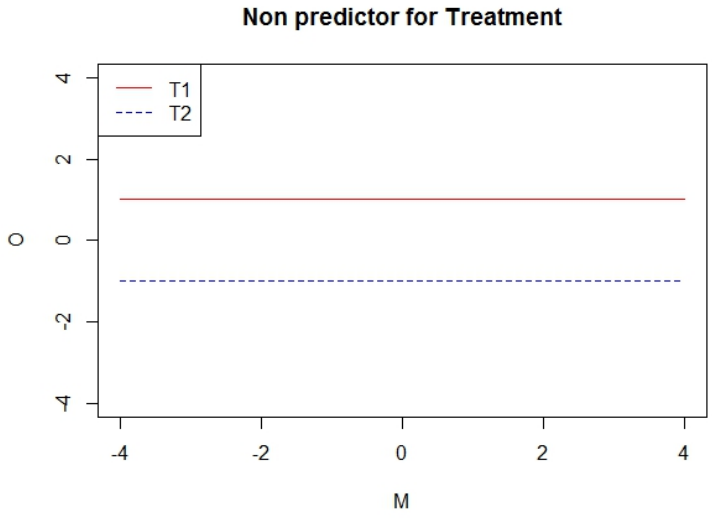

Figure 2.1: M Non Predictor

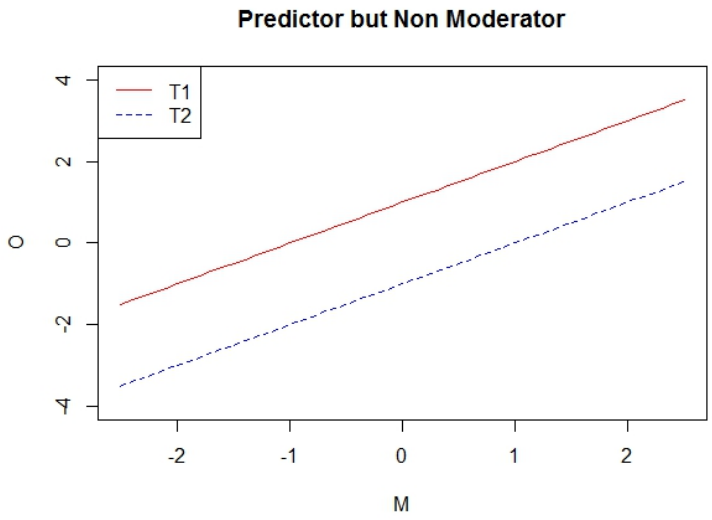

Figure 2.2: M Predictor Non Moderator

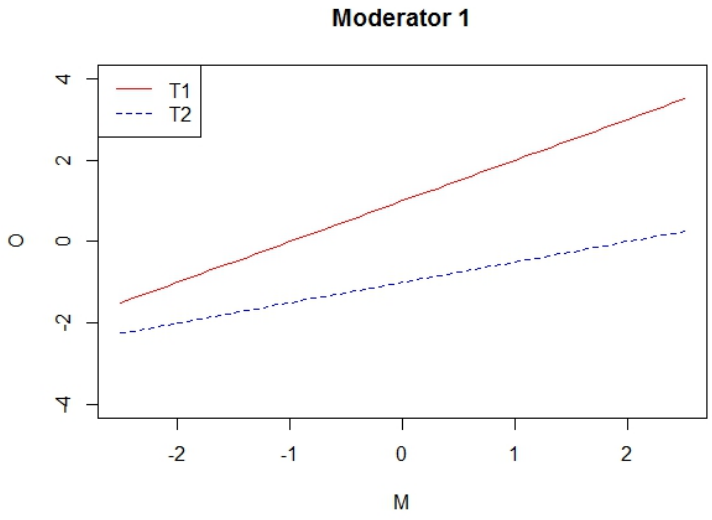

Figure 2.3: M Moderator Case 1

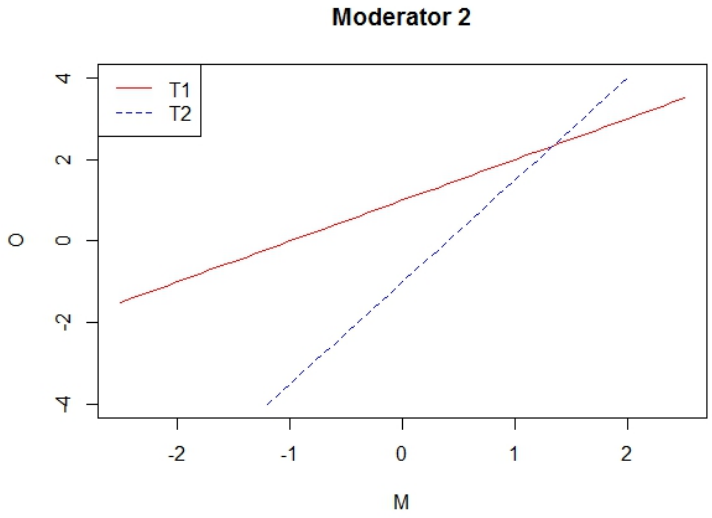

Figure 2.4: M Moderator Case 2

2.3 Single Moderator Calculation

Some have suggested using the interaction term $T * M$ to measure the effect of moderation. However this can be problems since when $M = -b_1/b_3$, the effect of treatment on O is 0. b_3 itself could not be moderator effect size mainly because when the measurement scale of O changes, the value of effect size will change accordingly while the real effect doses not actually change.

Some modifications on b_3 can be applied to solve the problem, such as using the standardized coefficient $d_i = b_i/\hat{\sigma}^2$ instead, where $i = 1, 2, 3$ and $\hat{\sigma}^2$ is the unbiased estimator for the variance of residuals. However, it is also unsatisfactory . There may be other relevant true moderators which are omitted from the model, and hence the moderator we focus on may not be the

moderator but happens to correlate with those omitted variables. The example used is that, if gender is treated as a moderator, the true moderator might be height, weight, or income. As a result, without introducing an instrumental variable, it is hard to determine whether the 'moderator' is a true moderator or just proxy one.

2.3.1 Moderator Effect size approach

According to the drawbacks, a moderator effect size method is utilized to test moderation in general case. It is plausible to consider the pairwise difference between randomly selected patients from $T1$ and $T2$ respectively, because the moderator will identify different outcome effects $(O_1 - O_2)$ of treatment groups on individuals.

We code $T1$ and $T2$ as -0.5 and 0.5 respectively, and we use the standardized coefficients d_i instead of original coefficients b_i. M is also scaled to have mean 0 and variance 1. Based on Equation 2.1, we have the outcome difference as

$$\triangle O = O_1 \text{ - } O_2 = b_1 + b_2(M_1 \text{ - } M_2) + b_3(M_1 + M_2)/2 + (\epsilon_1 \text{ - } \epsilon_2)$$

Define the average and difference effect as AM and DM, written as

$$AM = (M_1 + M_2)/2$$

$$DM = (M_1 - M_2)$$

Since M_1 and M_2 come from the same distribution and AM and DM are uncorrelated, the correlation coefficient between $\triangle O$ and AM is calculated

as

$$r(\triangle O, AM) = \frac{Cov(\triangle O, AM)}{Var(\triangle O)Var(AM)} = \frac{b_3/4\sigma}{(b_2^2/\sigma^2 + b_3^2/4\sigma^2 + 1)^{1/2}},$$

with

$$\begin{aligned} E(AM) &= 0 \\ E(\triangle O) &= b_1 + b_2 E(DM) + b_3 E(AM)/2 = b_1 \\ Var(AM) &= 1/2 \\ Var(\triangle O) &= 2b_2^2 + b_3^2/2 + 2\sigma^2 \\ Cov(\triangle O, AM) &= E(\triangle O \times AM) = b_3 E(AM)^2/2 = b_3/4. \end{aligned}$$

Similarly, the correlation coefficient between $\triangle O$ and DM is calculated as

$$r(\triangle O, DM) = \frac{Cov(\triangle O, DM)}{Var(\triangle O)Var(DM)} = \frac{b_2/\sigma}{(b_2^2/\sigma^2 + b_3^2/4\sigma^2 + 1)^{1/2}},$$

with

$$\begin{aligned} E(DM) &= 0 \\ E(\triangle O) &= b_1 + b_2 E(DM) + b_3 E(AM)/2 = b_1 \\ Var(DM) &= 2 \\ Var(\triangle O) &= 2b_2^2 + b_3^2/2 + 2\sigma^2 \\ Cov(\triangle O, DM) &= E(\triangle O \times DM) = b_2 E(DM)^2 = 2b_2. \end{aligned}$$

The correlation $r(\triangle O, AM)$ and $r(\triangle O, DM)$ can be written as

$$r(\triangle O, AM) = \frac{d_3}{2(d_2^2 + d_3^2/4 + 1)^{1/2}}$$
$$r(\triangle O, DM) = \frac{d_2}{(d_2^2 + d_3^2/4 + 1)^{1/2}}.$$

2.3.2 Measurement on Moderator Effect Size

Based on the discussion in Section 2.1.2, it is reasonable to determine the type of M using $r(\triangle O, AM)$ and $r(\triangle O, DM)$, whose ranges are both from -1 to 1, with a larger absolute value indicating a stronger moderator effect.

Cohen′s d can be re-formulated using $r(\triangle O, AM)$ and $r(\triangle O, DM)$ and used as the overall effect size comparing $T1$ and $T2$. As defined earlier,

$$Cohen^{'}s\ d \quad = \quad \frac{d_1}{(d_2^2 + d_3^2/4 + 1)^{1/2}},$$

where d_1 is the main effect of treatment, the Cohen′s d computing the difference between $T1$ and $T2$ at M=0. It is easy to see that

$$Cohen^{'}s\ d \quad = \quad d_1(1 - r(\triangle O, AM)^2 - r(\triangle O, DM)^2),$$

which is an equivalent formula with the previous definition. We now restate the three types of M based on the correlations:

1. **M: Non-predictor in both treatment groups** (T1 and T2)
   If $r(\triangle O, AM) = r(\triangle O, DM) = 0$, then it means M is non-predictor in both treatment groups, as is shown in Fig 2.1 . Cohen′s d is constant.

2. **M: Predictor but non-moderator in both treatment groups** (T1 and T2)

   If $r(\triangle O, AM) = 0$ but $r(\triangle O, DM) \neq 0$, then it means M is a predictor but non moderator in both treatment groups, and the treatment effect is the same for any value of M, as is shown in Fig 2.2. Cohen$'$s d is smaller than d_1, because M increases the within group variance, hence reducing the nonoverlap of the two groups.

3. **M: Moderator in both treatment groups** (T1 and T2)

   However, if $r(\triangle O, AM) \neq 0$, then it means M is a moderator in both treatment groups, and the effect size differs as M varies. Possible cases are shown in Fig 2.3 and Fig 2.4. Cohen$'$s d and d_1 are not satisfactory to show the treatment effect size within the population and thus $r(\triangle O, AM)$ plays an important role in interpreting the moderator effect size and making decisions.

Chapter 3

Multiple Moderators

3.1 Optimal Moderator Approach

The moderator effect size can be applied to detect the existence and strength of moderation based on $r(\triangle O, AM)$. For a single moderator, the bootstrap might be used to construct a confidence interval for $r(\triangle O, AM)$. However, if there are multiple moderators, based on moderator effect size tests, it is appealing to find an optimal moderator by combining those multiple moderators.

It is better to search for an optimal moderator instead of individual ones mainly because individual moderators can be all weak while the optimal one may provide strong moderation. In addition, without combining multiple moderators, it can be confusing to determine treatment according to separate individual moderators since they may be conflicting. The multiple moderators should be primarily focused on baseline variables, based on which the outcomes differ between treatment effects. Two different methods will be introduced to search and build an optimal moderator.

3.2 Development of an Optimal Moderator

3.2.1 Principal Component regression

Suppose $M = (M_1, \ldots, M_p)$ represent p potential individual moderators which have been standardized. To find the optimal moderator out of multiple moderators, it is equivalent to seek for optimal linear combination of $\alpha^{'}M$ for some vector α so as to maximize the interaction term b_3 in the following equation:

$$O = b_0 + b_1 T + b_2(\alpha^{'}M) + b_3 T * (\alpha^{'}M) + \epsilon \tag{3.1}$$

Let $\Phi_M = HDH^{'}$ denote the covariance matrix of M, where D is diagonal matrix of eigenvalues and H is orthogonal matrix. Define Φ_{MO_1} and Φ_{MO_2} to be the vector covariances between the outcomes and the p moderators corresponding to each treatment. Using principle component regression, the squared interaction term is $\alpha^{'}A\alpha$, with

$$A = D^{-1/2}H^{'}(\Phi_{MO_1} - \Phi_{MO_2})(\Phi_{MO_1} - \Phi_{MO_2})^{'}HD^{-1/2} \tag{3.2}$$

Hence we know the optimal linear combination turns out to be $\alpha^{'}M = \alpha_{\star}^{'}D^{-1/2}H^{'}M$, where $\alpha_{\star}$ denotes new matrix formed by selected eigenvectors whose corresponding eigenvalues of A are positive. In this way the optimal moderator is defined.

3.2.2 Regression Weights Based on Randomly-Paired Treatment Groups

In what follows are the steps for another approach to construct an optimal moderator:

1. **Eliminating multicollinearity among multiple moderators**

   Since the number of potential moderators may not be too small, multicollinearity problem can occur. Hence principal component analysis on all the baseline moderators turns to be a simple way to eliminate multicollinearity, and just select probable moderators whose eigenvalues are larger than 1.

2. **Calculating weights by regression on randomly-paired treatment groups**

   From the original data set, suppose the two treatments are $T1$ and $T2$ with $N1$ and $N2$ units respectively. A new data set is constructed by randomly pairing every unit in $N1$ group with every unit in $N2$ group, to get the final $N1 \times N2$ pairs in total. Thus the linear regression model is built as

   $$\triangle O = O_1 - O_2 \sim AM_i$$

   where $\triangle O$ is the outcome difference on each pairs between two treatments, and $AM_i = (M_{i1} + M_{i2})/2$ representing for the mean of every selected moderator variable for each pair. Each of the regression coefficients is then the weight, w_i, corresponding to the each potential moder-

ator from the linear model. Denote the optimal moderator by $M^\star$. For for $j = 1$ and $j = 2$ in each treatment group,

$$M^\star = \sum w_i M_{ij}$$

3. **New effect size for $M^\star$**

   Similar to the earlier approach, but using the optimal moderator $M^\star$ instead, the new effect size can be calculated by the linear regression model below

$$O = b_0 + b_1 T + b_2 M^\star + b_3 T * M^\star + \epsilon. \tag{3.3}$$

   Using d_i as the standardized coefficient, the optimal moderator effect size is calculated as

$$r(\triangle O, AM^\star) = \frac{d_3}{2(d_2^2 + d_3^2/4 + 1)^{1/2}}.$$

Chapter 4

Example

4.1 Data Description

The data comes from the study, approved by the University of Florida Institutional Review Board and delivered via Cooperative Extension Offices, of lifestyle interventions in treating rural obesity. An RCT was performed to determine the effects of three levels of behavioral lifestyle treatments in comparison to a control level with nutrition education, based on 6-month and 24-month body weight changes.

For convenience of the moderation analysis, we focused on the percent weight change as primary outcome from 0-month (baseline) to 6-month only, and combined the control condition (SLOW) and low level of treatment (LOW) as Treatment 1 (T1) while the moderate (MOD) and high (HIGH) levels as Treatment 2 (T2). T1 mainly involved deliveries of instructive information and lectures in healthy diet and appropriate physical exercise together with corresponding group discussions. T2 included the same contents of intervention at a higher delivery rate and extra behavior care such as goal setting and material incentive. This grouping method is reasonable in that the percent weight changes together with their 95% percent Confidence Interval for each

two treatments within T1 and T2 are close, in the period from baseline to 6-month (Table 1).

	SLOW(n=169)	LOW(n=148)	Moderate(n=134)	High(n=161)
6-month	4.1 (3.1 to 5.1)	7.2 (6.1 to 8.3)	9.3 (8.2 to 10.3)	10.9 (9.8 to 11.9)

Table 4.1: Percent of Weight Loss in 6-month

From ten rural counties in northern Florida, 1072 adults who responded to study announcements and met eligible criteria were screened. 460 of them were excluded due to failure in participation or medical eligibility and hence the rest 612 adults were selected and randomly assigned to T1 and T2 (Figure 4.1). Those participants were all in age between 21 and 75, with a body-mass index (BMI, kg/m^2) between 30 and 45, and had weight changes less than 4.5 kg in the previous 6 months.

4.2 Results and Interpretations

In order to determine individual moderators among all the baseline variables, as well as to find the optimal moderator if multiple moderators exist, the method of regression weights on Randomly-Paired Treatment Groups was applied to explore moderation here.

First we selected 10 baseline variables to be included in the model, after centering and scaling. Among these 10 baseline variables which are shown in Table 4.2, 400m-walk-time means the time used to walk 400 meters; $BAECKE_AF_0$, the Baecke questionnaire; and the other eight, quality

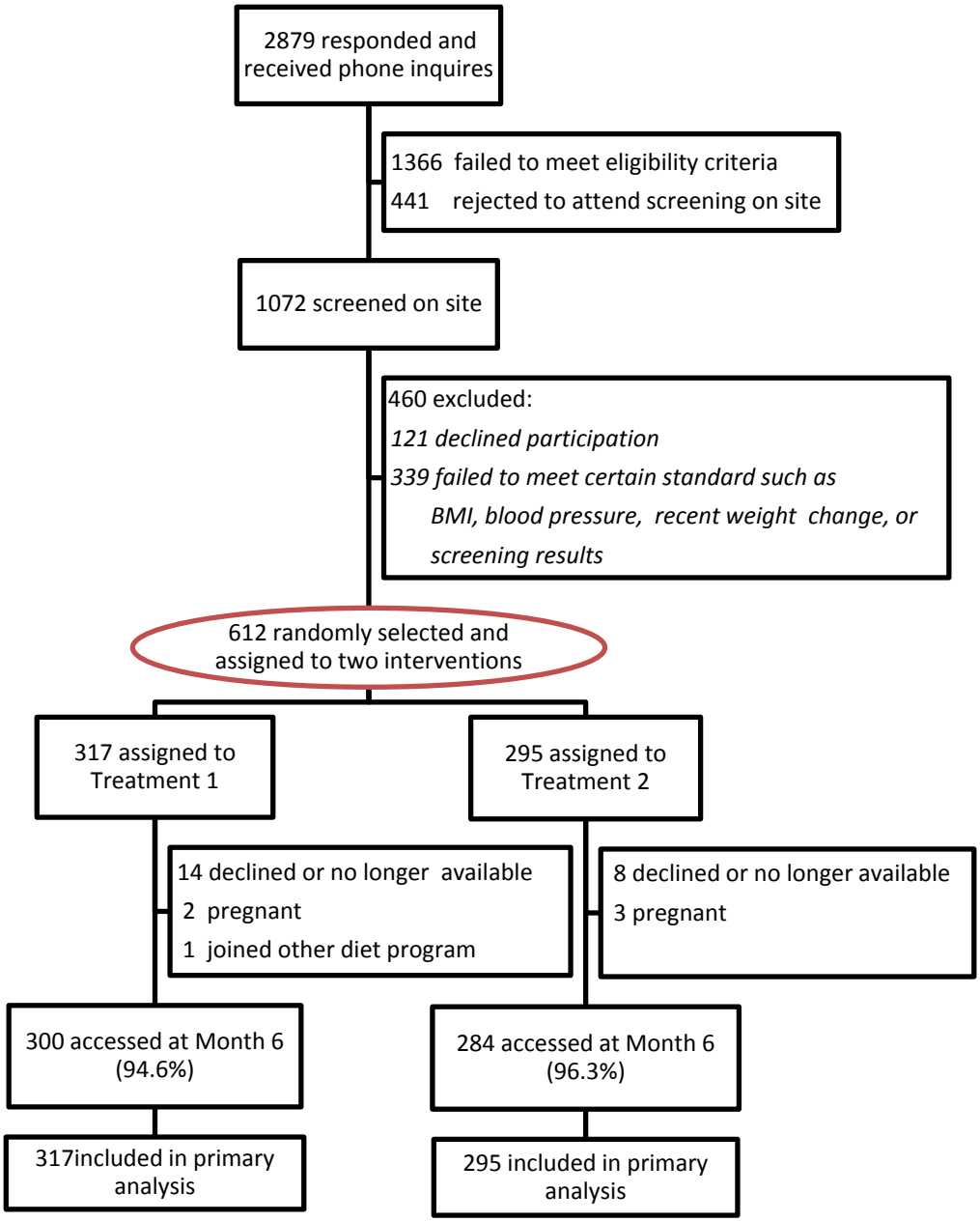

Figure 4.1: Participant flow from screening, random assignment, to follow-up in first 6 month

of life scales. The moderator effect size $r(\triangle O, AM)$ was calculated for each potential moderator and 8 of them were selected in calculating the combined moderator, with the other 2 deleted due to a low effect size (<0.01). We skipped the principle component analysis step here. The single moderator effect sizes are also shown in Table 4.2, from which we could tell that none of the 8 potential individual moderators had an effect size greater than 0.07. Thus, a combined multiple moderator would be desirable to increase strength and power of the moderation.

The Next step is to determine the weight of each individual moderator in the optimal one based on regression coefficients in Randomly-Paired Treatment Group. We constructed a new data set with Randomly-paired group from each treatment omitting the missing data, to get 40170 pairs in total, with dependent variable $\triangle O = O_1 - O_2$ for every pair, and eight potential moderators. Then the regression coefficients represent the weights (w) for the combined multiple moderators we computed (see Table 4.2).

After computing the weights, we construct an optimal moderator $M^\star$ by multiplying each potential moderators with their weights and then adding those terms together. The moderator effect size is -0.148 with 95% CI as $[-0.149, -0.145]$, which is much stronger than the individual effect size. The 95% CI seems kind of narrow which may be relative to the sample size.

To interpret the results, we look at the plot in Figure 4.2 where the percent of weight loss given $M^\star$ for $T1$ and $T2$ is shown. In the figure, the regression line for $T1$ interacts with that of $T2$ at a cross point for $M^\star = 2.66$.

Single Moderator	Moderator Effect size $(r(\triangle O, AM^{\star}))$	Weight in Moderator Combination(w)
SF_HT_0	-0.06	0.55
SF_RFP_0	-0.07	2.05
SF_BP_0	0.04	-0.71
SF_GH_0	-0.01	1.06
SF_VT_0	-0.02	0.62
SF_SF_0	0.06	-1.40
SF_MH_0	-0.07	0.84
$400m - walk - time$	-0.01	0.58
Ignored Moderator with low effect size		
$BAECKE_AF_0$	-0.005	
SF_RFE_0	-0.006	

Table 4.2: Single Moderator Effect Sizes and Weights in Combined (Optimal) Moderator

Since in the left part of the cross point (or line), the line of $T2$ is above $T1$, suggesting that $T2$ is better than $T1$ in weight loss while in the right part, $T1$ is above and hence more preferable than $T2$. Thus, based on the value of $M^{\star}$, we may implement different treatments on different people to achieve a better outcome.

In practice, when $M^{\star}$ is smaller than 2.66, then T2 is more desirable while on the other hand, when $M^{\star}$ is greater than 2.66, $T1$ is more desirable. Looking back to the data, only two participants have $M^{\star}$ greater than 2.66. Thus, we could probably not recommend $T1$ for anyone here.

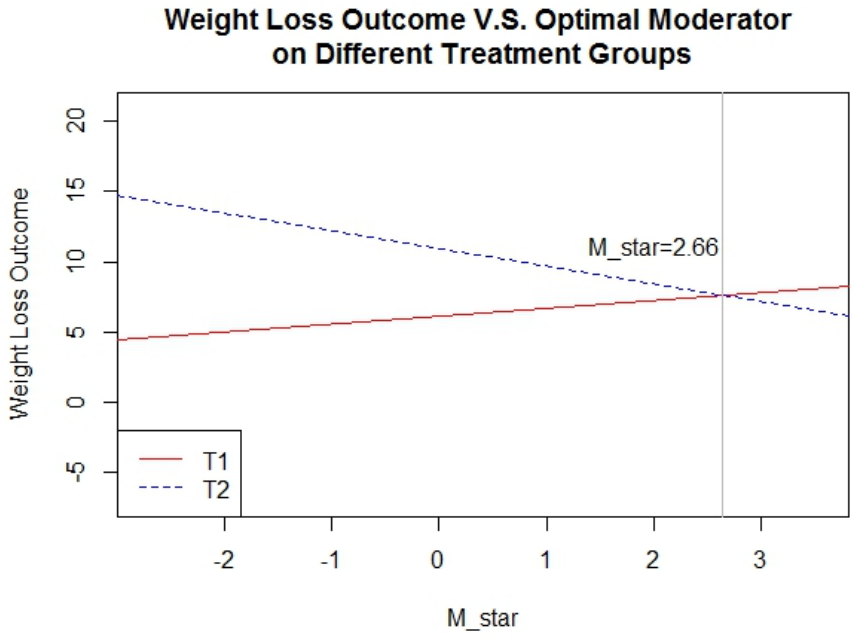

Figure 4.2: Moderation on T1 and T2

4.3 Discussion

This report discussed the methodology of individual moderator effect size calculation together with possible combined multiple moderators approach, using an RCT of weight loss for illustration. Moderation should be carefully considered in clinical treatments since it might reflect better the desire of different treatments from different patient groups. Moreover, the optimal moderator, which is calculated based on multiple moderator combination, holds a meaningful approach to the quantitative measure on judging which treatment is more preferable. It also account for most of the information from

individual moderators and provides simple guide for treatment selection.

However, there are some issues with the approach that was used. First, the weights we calculate in the combination dose not reflect the strength of moderation; that is, a moderator with small weight can still have a strong individual moderation. Second, moderators and optimal moderator are based on the selection of baseline variables, which is dependent on the missingness of the data and the elimination of multicollinearity among those variables. When facing lots of potential moderators, they should be fairly considered. Third, there are still many other ways to calculate the optimal moderator $M^\star$ and the exact value of cross point, and $M^\star$ may vary in terms the choice of calculation method.

Bibliography

[1] *2013 59th ISI World Statistics Congress on Modeling Strategies for Developing Treatment Response Indices.*

[2] Moderation: Tests for interaction in multiple regression. Available at `http://www.sagepub.com/upm-data/47569_ch_15.pdf`.

[3] Reuben M. Baron and David A. Kenny. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, 51(6):1173–1182, 1986.

[4] Lee A. Becker. *Effect Size (ES).* Available at `http://www.uccs.edu/lbecker/effect-size.html#Rosnow&Rosenthal`.

[5] Helena Chmura Kraemer, Michaela Kiernan, Marilyn Essex, and David J Kupfer. How and why criteria defining moderators and mediators differ between the baron & kenny and macarthur approaches. *Health Psychology*, 27(2S):S101, 2008.

[6] Lawrence Joseph. *Interactions in Multiple Linear Regression.* Available at `http://www.medicine.mcgill.ca/epidemiology/joseph/courses/EPIB-621/interaction.pdf`.

[7] David A. Kenny. *Moderation.* Available at `http://davidakenny.net/cm/moderation.htm#GO`.

[8] Kraemer and Helena Chmura. Discovering, comparing, and combining moderators of treatment on outcome after randomized clinical trials: a parametric approach. *Statistics in medicine*, 32(11):1964–1973, 2013.

[9] Michael G Perri, Marian C Limacher, Kristina Castel-Roberts, Michael J Daniels, Patricia E Durning, David M Janicke, Linda B Bobroff, Tiffany A Radcliff, Vanessa A Milsom, Chanmin Kim, et al. Comparative effectiveness of three doses of weight-loss counseling: Two-year findings from the rural lite trial. *Obesity*, 22(11):2293–2300, 2014.